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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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07/20/2001

Jiro Hitomi

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EXAMINER

HADDAD, MAHER M

ART UNIT

PAPER NUMBER

1644

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/910,208	<b>Applicant(s)</b> HITOMI ET AL.	
	<b>Examiner</b> Maher M. Haddad	<b>Art Unit</b> 1644	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on 04 March 2008.

2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) 18-26 is/are pending in the application.

    4a) Of the above claim(s) 24-26 is/are withdrawn from consideration.

5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.

6) ☒ Claim(s) 18-23 is/are rejected.

7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.

8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All    b) ☐ Some \*    c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
    Paper No(s)/Mail Date \_\_\_\_\_.

4) ☐ Interview Summary (PTO-413)  
    Paper No(s)/Mail Date \_\_\_\_\_.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: \_\_\_\_\_.

## RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/4/08, is acknowledged.
2. Claims 18-36 are pending.
3. Claim 24-26 is withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

In view of Applicant's cancellation of SEQ ID NOs: 20 and 12, the examiner extended the search to cover antibody that binds SEQ ID NO: 19 encoded by SEQ ID NOS: 1.

4. Claims 18-23 are under consideration in the instant application as they read on an antibody with binding affinity to a protein encoded by SEQ ID NO: 1.

5. The amendment filed 3/27/07 stands objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment filed on 3/27/07 to the computer readable form of the "Sequence Listing" with SEQ ID NO: 19 and 20 represents a departure from the specification and the claims as originally filed. Applicant does not point out for support for the newly added sequences. It is noted that the new SEQ ID NO: 19 contains <sup>17</sup>Glu, which was not found in original SEQ ID NO: 19 (<sup>17</sup>Gln). Further, new SEQ ID NO: 20 contains <sup>65</sup>Asn, which was not found in original SEQ ID NO: 20 (<sup>65</sup>Gln). The specification and the claims as originally filed have no support for the new replacement of SEQ ID NO: 19 and 20.

6. In view of the amendment filed on 3/4/08, only the following rejections are remained.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

8. Claims 18-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrases "SEQ ID NO: 19 or 20) claimed in claims 18 and 21 and "these lineages" claimed in claim 22, line 3 represents a departure from the specification and the claims as originally filed.

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Applicant's amendment filed 3/27/07 and 12/4/06 does not point to the specification for support for the newly added limitations "SEQ ID NO: 19" claimed in claims 18 and 21 and "these lineages" as claimed in claim 22. It is noted that the new SEQ ID NO: 19 contains <sup>17</sup>Glu, which was not found in original SEQ ID NO: 19 (<sup>17</sup>Gln). However, the specification does not provide a clear support of such limitation. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

Applicant's arguments, filed 3/4/08, have been fully considered, but have not been found convincing.

Applicant submits that the original sequence ID provided to the Office and the subsequent sequence ID provided to the Office on 3/7/07 are identical. However, the sequence ID provided to applicant by the Office dated 12/6/06 is inaccurate and is responsible for the inconsistencies pointed out by the Examiner.

However, the Examiner notes that (1) Fig. 1 and 2 depicts amino acid of 17 as Gln (Q) not Glu (E) as claimed. (2) the parent application 09/270,455, now Pat 6,313,267 and 08/568,310 12/06,310, now 5,976,832 list position 17 of SEQ ID NO: 19 as Gln (Q) not as Glu (E) as claimed. (3) SEQ ID NO: 1 encoding SEQ ID NO: 19 in the "Sequence Listing" lists the codon CAG which code for Gln (Q) not Glu (E) as claimed. (4) SEQ ID NO: 1 does not encode SEQ ID NO: 19. Applicant did not provide any evidence that the newly added SEQ ID NO: 19 is the accurate one.

9. Claim 22 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody with binding affinity to a calcium-binding protein comprising an amino acid sequence encoded by SEQ ID NO: 1 or 12 for diagnosing inflammatory diseases, dermatosis and lung and skin cancer, a method for producing a monoclonal antibody, and a calcium-binding protein assay reagent comprising said antibody; does not reasonably provide enablement for a diagnostic agent for inflammatory diseases, "neoplastic diseases", dermatosis or "blood diseases of PMN, macrophages" and these lineages, which comprises an antibody of claim 18, in claim 22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Actions.

Applicant's arguments, filed 3/4/08, have been fully considered, but have not been found convincing.

The Declaration of Dr. Hitomi under 37 CFR 1.132, filed 3/4/08 is insufficient to overcome the enablement rejection of claim 22 because the declaration refers to Fig. 2, 3, 4. However, no such Figure can be found in the declaration. Further, the scope of the claims is much broader than the what has been shown in the declaration. Finally, the claims are drawn to antibodies that bind to bovine CAAF1, while the Declaration uses anti-hCAAF1 antibody.

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12. The following new ground of rejections are necessitated by the amendment submitted 3/04/08.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

11. Claim 18-19 and 22-23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Guignard *et al* (European Journal of Clinical Investigation, Vol:24, Supl. 2, pp.211, 1994), as is evidenced by Guignard *et al* (July 1995), Yamamura *et al* and the specification on page 2 lines 7-35 and instant specification.

Guignard *et al* (1994) teach a polyclonal antibody (anti-P8 or anti-MRP-8), identify an unknown protein of 6.5 kDa (P6). Guignard *et al* also teaches that the P6 protein identified by N-terminal amino acid sequence analysis appeared to be a new protein of the S100 family (calcium-binding proteins). Further, Guignard *et al* concluded that a new protein of 6.5 kDa belonging to the S100 family was evidenced in human neutrophils (see abstract in particular). While the Guignard *et al* is silent as to the "bCAAF1" *per se*; P6 has the same N-terminal amino acid sequence encoded by hCAAF1 as is evidenced by Guignard *et al* (1995) that the p6b N-terminal sequence (p6b) TKLEEHLEGIVNIFHQYSVR (see Figure 3, at page 398 in particular) which is 100% identical to amino acids 2-21 of the amino acid encoded by hCAAF1. Further evidence that the amino acid sequence encoded by hCAAF1 is p6 protein came from Yamamura *et al* who teach that Guignard *et al* (1995) isolated and partially characterized a novel human calcium-binding protein that cross-reacted with an antibody against MRP8. Yamamura *et al* concluded that the identified N-terminal 20 amino acid sequence of the reported protein was identical to that of human CAAF1, suggesting that this protein is hCAAF1 (see page 359, lines 4-8 in particular). Given that the human and the bovine CAAF1 share 66% identity, the reference polyclonal antibody would bind to bovine CAAF1 in the absence of evidence to the contrary.

It is noted that MRP-8 (S100A8) shares only 40% sequence homology to the human S100A12 (hCAAF1). Yet, anti-MRP-8 antibodies cross-react with the human CAAF1).

Further evidence is provide by Applicant's specification on page 40, lines 6-9 that the existence of antigen reacting with CAAF1-22-5 monoclonal antibody in human tissue strongly suggests the existence in human tissue of a protein (human CAAF1) homologous with bovine CAAF1. Accordingly, given the high sequence identity/homology (66%) between the referenced/claimed P6 protein; the referenced antibodies would have the inherent property of binding bovine CAAF1 in the absence of objective evidence to the contrary. Moreover, given that the antibody raised against S100A8 (Guignard *et al*, 1995) cross-reacted with P6 (human CAAF1), the reference antibody would bind to claimed bovine CAAF1, in the absence of evidence to the contrary.

The reference teachings anticipate the claimed invention.

12. Claim 18-20 and 22-23 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kelly *et al* (J. Pathol. 1989).

Kelly *et al* teach monoclonal antibodies to study the expression of calgranulins by keratinocytes in inflammatory dermatoses. Kelly *et al* also teach that calgranulins are intracellular calcium binding proteins which have inflammatory cytokine activity. Further, Kelly *et al* teach that MAC 387 monoclonal antibody that recognizes a molecule probable containing both calgranulin A and B (see abstract in particular). MAC 387 monoclonal antibody also binds amino acid sequence encoded by SEQ ID NO: 19, as is evidenced by Guignard *et al* (Feb 1996) that the immunoreactivity of MAC 387 was compared with that of a polyclonal antibody raised against purified MRP-8, but cross-reacting with MRP-14, and p6 (hCAAF1/S100A12), a novel S100 protein. Under such conditions, Mac 387 was found to recognize the three S 100 proteins (see abstract in particular). Given that the human and bovine CAAF1 share 66% sequence homology, the reference MAC 387 would bind the claimed bovine sequence, in the absence of evidence to the contrary.

Applicant's arguments, filed 3/4/08, have been fully considered, but have not been found convincing.

Regarding Applicant's comment with respect to Yamamura reference, the examiner notes that the critical date of extrinsic evidence showing a universal fact need not antedate the filing date. See MPEP § 2124.

13. Claims 18-20 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dell'Angelica (JBC, 269(46): 28929-28936, 1994) as evidenced by the specification disclosure on page 40, lines 6-9, Bost *et al*. (Immunol. Invest. 1988; 17:577-586), in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1).

Dell'Angelica *et al* teach the primary structure (see Fig. 4) and binding properties of pig calgranulin C, S100-like calcium-binding protein from pig granulocytes. Dell'Angelica *et al* teach that the pig calgranulin C consists of 91 residues. Sequence analysis predicts two EF-band calcium-binding motifs (see Fig. 8), the first having an extended loop that is distinctive of the S100 protein family. Dell'Angelica *et al* teach that their results and the calcium-dependent binding of the protein to a phenyl-Superose column strongly suggest that calgranulin C undergoes a gross conformational change upon calcium binding thus supporting the idea that this protein may be involved in Ca<sup>2+</sup>-dependent signal transduction events (see abstract). The

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reference pig calgranulin C sequence has 79% sequence identity to claimed SEQ ID NO: 19. See below:

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Qy      1 MTKLEDHLEGIINIFHEYSVRVGHFDTLNKRELKQLITKELPKTLQNTKDKQPTIDKIFQD 60
      |||||
Db      1 MTKLEDHLEGIINIFHQYSVRLGHYDTLIKRELKQLITKELPNTLKNTKDQGTIDKIFQN 60
      |||||
Qy      61 LDADKDGAVSFEEFVVLVSRVLKTAHIDIHKE 92
      |||||
Db      61 LDANQDEQVSFKEFVVLVTDVLTAHDNIHKE 92
      |||||

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The claimed invention differs from the reference teachings only by the recitation of an antibody specific to a calcium-binding protein comprising an amino acid sequence shown in SEQ ID NO. 19 or encoded by a nucleic acid sequence shown in SEQ ID NO: 1 in claim 18, which is a polyclonal antibody or monoclonal antibody in claim 19, a hybridoma in claim 20, an agent comprising the antibody in claim 22, a reagent comprising the antibody in claim 23.

However, it has been held that once the antigen of interest is selected, the use of that antigen in the known method of Kohler and Milstein will result in the expected hybrid cell lines and the specific monoclonal antibodies. Ex parte Erlich, 3 USPQ2d 1011, 1015 (BPAI 1986).

Moreover, Campbell teaches that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (see page 3 figure 11.1 in particular). One field of research in which monoclonal antibodies may prove of particular value is in the study of chromosomal proteins. The search for those chromosomal proteins which are responsible for determining cell phenotype has been particularly long and comparatively fruitless and monoclonal antibodies are ideal tools for the dissection of the complex mixture of proteins. As hybridoma production becomes a more routine laboratory technique (see page 29 and 30 under Basic research in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a monoclonal antibody as taught by Campbell against the pig calgranulin C taught by Dell'Angelica et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because it was customary at the time the invention was made to make monoclonals against any new macromolecule as taught by Campbell.

The resultant antibody would bind to the bovine CAAF1 of SEQ ID NO: 19 as is evidenced by Applicant's specification on page 40, lines 6-9 that the existence of antigen reacting with CAAF1-22-5 monoclonal antibody in human tissue strongly suggests the existence in human

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tissue of a protein (human CAAF1) homologous with bovine CAAF1. It is noted that human and bovine share only 66% sequence homology. Given the high sequence identity/homology between the referenced/claimed polypeptides (79%); the resultant antibodies would have the inherent property of binding bovine CAAF1 polypeptide of SEQ ID NO: 19 in the absence of objective evidence to the contrary.

Further evidence came from Bost *et al* that an antibody "cross-reacts", i.e. binds to more than one protein sequence, mean that "specifically bind" with both proteins. Bost *et al* (Immuno. Invest. 1988 ;17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues were identical (see entire document, especially the Abstract and Discussion).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 30, 2008

/Maher M. Haddad/  
Primary Examiner,  
Art Unit 1644